

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PARSE BIOSCIENCES, INC.,
Petitioner

v.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR
UNIVERSITY,¹
Patent Owner

Case IPR2023-01033
Patent 10,738,357

**PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

¹ Petitioner listed 10x as the Patent Owner. While 10x, as exclusive licensee, is the real party-in-interest, The Board of Trustees of the Leland Stanford Junior University (“Stanford University”) is formally the Patent Owner.

LIST OF EXHIBITS

Exhibit	Description
EX2001	File History of App. No. 14/784,250
EX2002	U.S. Patent Pub. No. 2015/0111788
EX2003	U.S. Patent No. 9,080,211
EX2004	S. Ma & Y. Zhang, <i>Profiling chromatin regulatory landscape: insights into the development of ChIP-seq and ATAC-seq</i> , Molecular Biomedicine (2020)
EX2005	T Shashikant & C. Ettensohn, <i>Genome-wide analysis of chromatin accessibility using ATAC-seq</i> , Methods Cell. Biol. 151:219-235 (2019)
EX2006	A. Han, <i>Parse Biosciences Expands Single-Cell Product Line</i> , Global Research, genomeweb (Apr. 14, 2022), (available at https://www.genomeweb.com/sequencing/parse-biosciences-expands-single-cell-product-line-global-reach)
EX2007	Henderson's Dictionary of Biology (Eleanor Lawrence ed., 14th ed., 2008)
EX2008	Bruce Alberts, et al., <i>Molecular Biology of the Cell</i> , Garland Science (4th ed. 2002)
EX2009	U.S. Patent Pub. No. 2015/0337298
EX2010	File History of App. No. 16/418,796
EX2011	Declaration of Sayem Osman
EX2012	U.S. Patent Pub. No. 2003/0032141
EX2013	File History of App. No. 16/418,889
EX2014	U.S. Patent Publ. No. 2011/0306042
EX2015	B. Audit et al., Open Chromatin encoded in DNA sequence in the signature of 'master' replication origins in human cells, Nucleic Acid Research, 37 (18), 6064-6075 (2009)
EX2016	Declaration of J. Steven Baughman

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I. Introduction

10x Genomics, Inc. (“10x”) submits this §42.107² Preliminary Response to the above-captioned Petition (“Petition”/“Pet.”). The Board should deny the Petition because it fails to meet Petitioner’s burden to establish unpatentability of claims 1-30 (the “Challenged Claims”) of U.S. Pat. No. 10,738,357 (the “’357 Patent”/“’357”).

Petitioner’s Grounds 1-3 present obviousness arguments based on Grunenwald and additional references. But those Grounds each have two threshold failures. First, Petitioner entirely fails to assert or analyze whether its references are analogous art *to the ’357* (instead discussing only whether they are analogous *to one another*). This failure impacts all three obviousness grounds and requires denial, as the Federal Circuit recently confirmed. *See, e.g., Sanofi-Aventis Deutschland GmbH v. Mylan Pharms. Inc.*, 66 F.4th 1373 (Fed. Cir. 2023) (reversing a Final Written Decision for this failure). Second, the Petition has multiple particularity failures, including: (1) repeated mis-cites to its references (including secondary reference Song); (2) reliance on disconnected Grunenwald embodiments without acknowledgement or explanation; and (3) invoking three

² Unless stated, all statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as context indicates, and all emphases/annotations are added.

permutations of “Ground 2” (Saleh and/or Song) without explaining each of these three “grounds” or how Saleh and Song, used for the same limitation, would be used in combination.

Even if these definitive failures were, *arguendo*, overlooked (they cannot be), Petitioner’s Grounds are each deficient for failing to show that the cited art discloses or renders obvious various claim limitations.³ For example, Petitioner relies on Okino to cover the requirement of a permeabilized cell nucleus, but points only to disclosures related to the cell membrane, not the cell nucleus. Thus, Petitioner fails to show Okino even *discloses* a permeabilized *cell nucleus*, let alone *permeabilizing* one with “NP40 or Tween detergents,” as Petitioner asserts as the basis for its obviousness arguments. Petitioner’s attempt to mask this deficiency by trying to draw parallels to the ’357 also fails, and cannot meet Petitioner’s burden.

In addition, Petitioner argues various additional limitations are “inherent” but fails to present any persuasive technical reasoning to explain its arguments, and

³ Petitioner’s Grounds 2-3 depend on Ground 1’s Okino and Grunenwald arguments for all four independent claims. Pet.8. Ground 3 covers independent claim 16, but only purports to modify the “first sequencing adapter and second sequencing adapter” limitation. Pet.62.

its mere conclusory assertions cannot carry its burden. Pet.29-33. For example, Petitioner argues claim 1's "a plurality of polynucleotide molecules" is inherently disclosed by Grunenwald, but admits in that same paragraph that "*almost all* eukaryotic organisms" have multiple chromosomes, conceding some do not, and thus this limitation is *not* inherent. Pet.32. Petitioner's other inherency arguments—that transposases will necessarily bind to open chromatin and will form a high affinity macromolecule complex—are similarly superficial and facially deficient. Pet.37-38, 54.

Petitioner also failed to show Grunenwald disclosed the *chromatin* limitations of independent claims 2, 16, and 22. Petitioner's argument is simply that "Grunenwald discloses contacting a cell, and thus a cell nucleus, directly with an insertional enzyme complex to accomplish tagmentation." Pet.37. But this fails to establish that Grunenwald discloses performing this method on a eukaryotic cell (the only cells with a nucleus) or that when performed on a eukaryotic cell the transposase would contact chromatin (which is found in the nucleus—the only cellular location in which chromatin exists). Pet.37-38.

Finally, Petitioner's supposed motivation to combine arguments fail. For Ground 1 Petitioner asserts POSITA would have been motivated to swap Grunenwald's disclosure of electroporation (which Petitioner asserts would *already* have allowed a transposase to access the nucleus) for Okino's detergents

(which Petitioner asserts would have permeabilized the nucleus to “better permit” transposase to enter the nucleus). Pet.29. But in so arguing, Petitioner fails to (1) identify a problem in Grunenwald that POSITA would have been motivated to solve or (2) explain how Okino would have “improve[d] access” to the nucleus. Petitioner’s Grounds 2 and 3 motivation to combine arguments are similarly perfunctory and superficial, and therefore insufficient to meet Petitioner’s burden for obviousness. *Salpeter v. ARP Wave, LLC*, IPR2019-01384, Pap.12, 16-17 (Jan. 27, 2020) (denying institution and stating that “[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements”) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

While the Petition’s merits failures warrant denial, the circumstances here also support denial as a separate threshold matter under §325(d). Grunenwald (the reference at the heart of each of Petitioner’s three Grounds) was not only of record during prosecution—which alone would satisfy part one of the §325(d) analysis—but it was ***the basis of an obviousness rejection*** and also ***discussed*** in and ***incorporated by reference*** into the ’357. Similarly, Petitioner’s four secondary references were either before the Examiner, discussed in ’357’s specification, or cumulative of references before the Examiner. Petitioner’s allegation of “error” (for part two of the §325(d) analysis) is simply that the Examiner erred “by not considering the relevant teachings in Grunenwald,” including its “application of

tagmentation to living cells *in vivo*,” and failed to consider Okino’s “disclos[ure of] permeabilization of the cell and nuclear membrane by the use of nonionic detergents, particularly NP40 and Tween20.” Pet.67-68. But Petitioner does not prove the Examiner misunderstood or overlooked either teaching. Petitioner entirely fails to explain how the Examiner could have failed to consider Grunenwald *when it was meaningfully analyzed in the Examiner’s asserted rejection and incorporated by reference into the ’357 itself*. Moreover, the Examiner acknowledged art regarding tagmentation in living cells in a rejection during prosecution of ’357’s related application. EX2001, 380-382, 437-438. And during prosecution of ’357 the Examiner also acknowledged permeabilizing a cell nucleus with NP40 and Tween 20 in the Jouvenot reference that the Examiner applied *in combination with Grunenwald*—a rejection the Applicant overcame. Petitioner simply ignores this prosecution history that directly contradicts Petitioner’s allegations of “error.” Thus, as a threshold matter, §325(d) denial is appropriate here to avoid squandering both the Board’s and 10x’s time and resources in rehashing arguments raised and resolved in prosecution.

II. Challenged Claims Are Directed To A Novel, Non-Obvious Invention

The ’357, “Transposition of Native Chromatin for Personal Epigenomics,” claims priority to a May 23, 2013 provisional application. EX1001, 1; Pet.12. The patent describes innovative compositions used in analyzing chromatin of a sample

of cells. EX1001, 45:1-46:51. The inventors of this patent coined the term “ATAC-seq” as the name of their method, which uses these compositions.

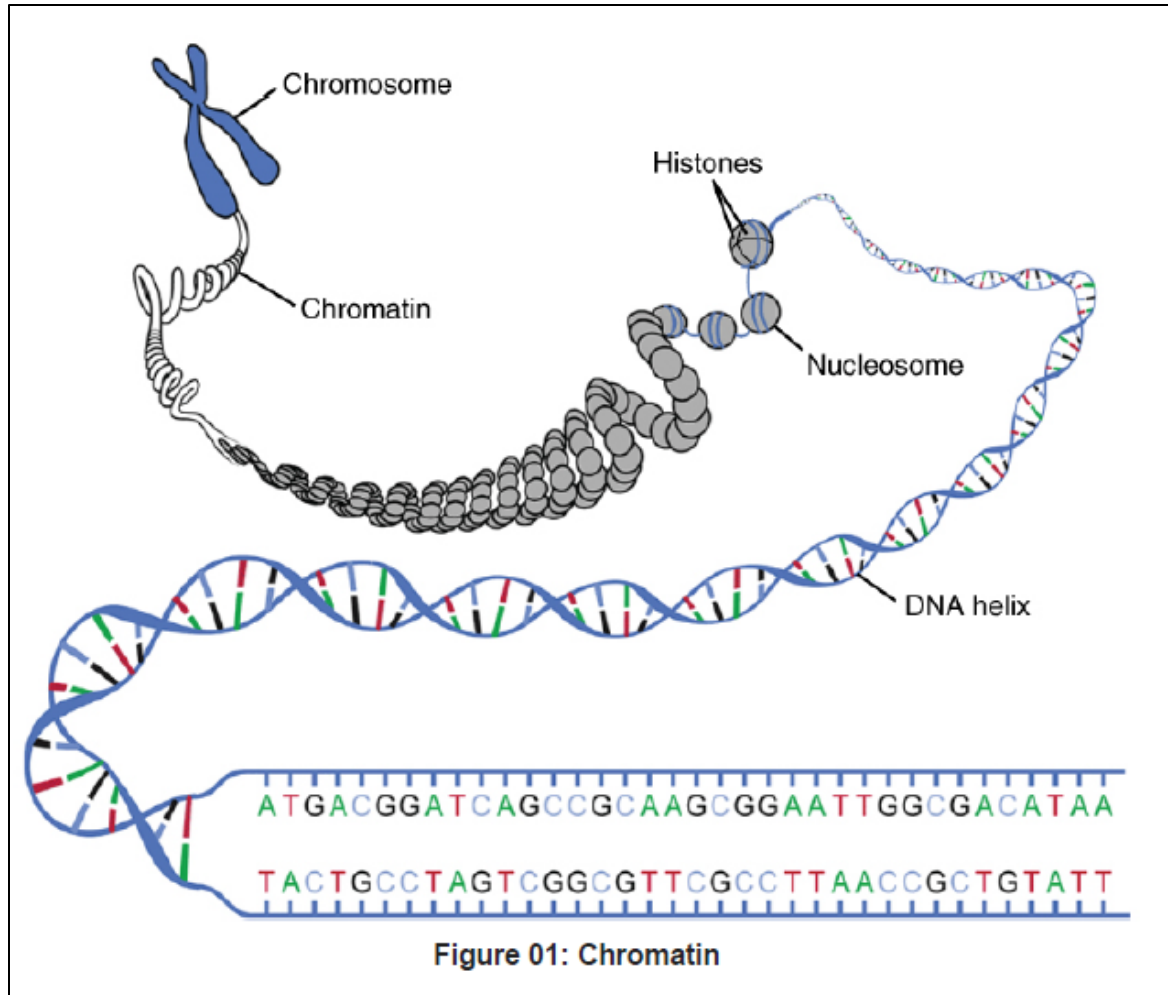
EX1001, 24:47-48. ATAC-seq stands for Assay for Transposase-Accessible Chromatin using sequencing. EX1001, 24:47-48. ATAC-seq is now the industry-standard term for their method due to its elegant simplicity. EX2004, 1, 6 (Fig.3); EX2005, 1, 4. Indeed, Parse itself refers to its planned competing product as an “ATAC-seq” product, and to this method as “ATAC-seq.” EX2006, 1-2.

“Eukaryotic genomes are hierarchically *packaged into chromatin*, and the nature of *this packaging* plays a central role in gene regulation.” EX1001, 1:29-31. And the ’357 underscores the critical importance—for epigenetic analysis—of the information conveyed by chromatin’s structural packaging, discussing the “[m]ajor insights into *the epigenetic information encoded within the nucleoprotein structure of chromatin* [that] have come from high-throughput, genome-wide methods for separately assaying the chromatin accessibility (‘open chromatin’), nucleosome positioning, and transcription factor (TF) occupancy.” *Id.*, 1:31-36.

As Petitioner’s own references explain, chromatin is found in (and only in) the cell nuclei of eukaryotes, and portions of the DNA in chromatin is organized by being condensed and tightly wrapped around proteins called “histones.” EX1036, 3; EX1041, 1. As the ’357 states, chromatin is:

a complex of molecules including proteins and polynucleotides (e.g. DNA, RNA), *as found in a nucleus* of a eukaryotic cell. Chromatin is composed in part of histone proteins that form nucleosomes, genomic DNA, and other DNA binding proteins (e.g., transcription factors) that are generally bound to the genomic DNA.

EX1001, 12:61-67; *see also id.* 17:22-24 (distinguishing genomic DNA from chromatin: “The polynucleotide can be genomic DNA. The polynucleotide can be further bound to proteins, such as histones, and may be *optionally packaged in the form of chromatin*”). Chromatin exists in a variety of forms that can be present at any given time, including heterochromatin and euchromatin. EX1041, 2; EX1036, 3; EX1001, 18:19-26, 24:51-56. Heterochromatin regions are tightly packed and condensed; euchromatin regions, often referred to as “open chromatin,” are relatively less condensed, which exposes particular genes for transcription into mRNA. EX1041, 2; EX1036, 3; EX1001, 4:58-61 (“Transposase... inserts only in regions of open chromatin”). The collection of chromatin forms a chromosome. EX1041, 1; EX1036, 4. The structure of chromatin is illustrated in the image below.



EX1041, 4 (Fig.1). In sum, only certain DNA is packaged with proteins in this fashion, and only eukaryotes have chromatin—and only in their cell nuclei.

EX1041, 2; EX1036, 3.

“[E]pigenetic information [is] encoded within the nucleoprotein structure of chromatin.” EX1001, 1:31-33. Epigenetics relates to modifications to a chromosome that impact what genes are transcribed to mRNA (which can then be expressed as proteins) *without* changing the chromosome’s DNA sequence—*e.g.*,

which portions of chromatin are “open” or not in a cell at any given time based on cellular signals and gene activity. EX1004, ¶¶3-4; EX1002, ¶¶82-85.

The Challenged Claims are directed to innovative compositions used to analyze chromatin in a sample of cells to assess an individual’s epigenome, comprised of *a permeabilized cell nucleus* with (1) *polynucleotides (which are one of the complex of molecules that make up chromatin)* and (2) an *insertional enzyme complex*. EX1001, 45:1-46:51. Independent claims 2, 16, and 22 explicitly require that the insertional enzyme complex contact/bind open chromatin or that the nucleic acids tagged by the insertional enzyme complex are derived from an open chromatin region. *Id.*

The ’357 is a continuation of App. No. 14/784,250—the first non-provisional application filed in ’357’s family, which issued as U.S. Patent 10,059,989 (“’989 Patent”/“’989”). During prosecution of the ’989’s application, the Examiner (the same as ’357’s) rejected certain claims as anticipated by U.S. Patent Publication 2015/0111788 to Fernandez *et al.* (“Fernandez”) (EX2002), and others as obvious based on Fernandez combined with additional references. EX2001, 380-385.

The Examiner argued that “Fernandez et al teach[es] wherein said chromatin is contacted with said insertional enzyme complex within said nucleus of said cell.” EX2001, 381. In an interview following this rejection, the applicant

proposed an amendment (to require that “the insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin”) and the Examiner indicated the Fernandez rejections would be withdrawn if this amendment were made. EX2001, 409, 421. Following the interview, applicant submitted the amended claims and an IDS, which identified U.S. Patent 9,080,211 to Grunenwald (EX2003) (the patent Petitioner’s EX1003 matured into) on its first page (EX2001, 401, 413)—after Grunenwald had *already* been referenced twice and incorporated by reference in the pending specification (EX1001, 13:26-33, 14:43) and identified in an earlier IDS (EX2001, 295). The Examiner then issued a Notice of Allowance, stating in the Reasons for Allowance that:

No prior art was found teaching or suggesting a method for analyzing chromatin comprising contacting chromatin from a nucleus of at least one cell with an insertional enzyme complex to produce a plurality of tagged fragments of genomic DNA, wherein said insertional enzyme complex does not comprise an antibody specific to a protein that is part of said chromatin... An updated search did not reveal any prior art against the claimed invention. In fact, the prior art teaches away from chromatin analysis as instantly claimed to obtain epigenetic information. Rather the art supports chromatin immunoprecipitation, which involves the use of an insertional complex that comprises an antibody specific to a protein that is part of the chromatin, as a main tool for investigating epigenetic marks... Accordingly, the instant invention is deemed novel and non-obvious over the prior art.

EX2001, 437-438.

Prosecution continued in various continuations, including the related Application No. 16/418,889 (the “’889 Application”), which issued as U.S. Patent No. 10,619,207 (the “’207”). The same Examiner allowed ’207’s claims, directed to methods of analyzing chromatin in permeabilized cell nuclei, without rejection, noting: “While the art teaches various aspect[s] of the instant invention, the prior art does not teach contacting the cell nucleus of the plurality of cell nuclei with a transposase complex such that polynucleotides of the cell nucleus are tagged at regions of open chromatin.” EX2013, 155.

And during later prosecution of the ’357, the Examiner rejected the then-pending claims as obvious over Petitioner’s Grunenwald (EX1003) in view of Jouvenot (EX2014) and Audit (EX2015). The Examiner argued Grunenwald disclosed a “composition comprising target DNA with a transposase and a transposon end” and the DNA may be “double stranded target DNA.” EX1007, 152-153. The Examiner also found that “Grunenwald et al do not expressly teach wherein the composition comprise of a permeabilized cell nucleus, but note[d] that composition may comprise of genomic DNA, subgenomic DNA, or chromosomal DNA such as isolated from chromosome or a portion of a chromosome ([0146]).” EX1007, 154-155. The Examiner then turned to Jouvenot, arguing it taught “a method and reaction mixture for analyzing chromatin structure and/or epigenetic

status in chromosomal DNA of a cell wherein the composition comprises permeabilizing nucleus of a cell to all for entry of an insertional enzyme” using “NP40, Tween 20 or Triton X-100” so as to not destroy the chromatin structure. EX1007, 155-156. The Examiner acknowledged that neither Grunenwald nor Jouvenot “expressly teach plurality of DNA or fragments derived from open chromatin regions,” but asserted it would have been obvious to modify Grunenwald to encompass a permeabilized cell nucleus as taught by Jouvenot. EX1007, 156.

Applicant responded that “none of the cited references teach or suggest a composition comprising a permeabilized cell nucleus, in addition to the other elements listed in the claims.” EX1007, 198 (emphases original). Applicant further argued that the rejection “merely identif[ied] elements of the pending claims in the cited art, and link[ed] them together with conclusory statements regarding their benefits, without first identifying the problem to be solved in the prior art.” EX1007, 200. The Examiner then allowed the claims, concluding that “[w]hile... Jouvenot... discloses a permeabilizing **cell membrane** such that the structure of genomic DNA of the cells” are not disrupted, “the prior art either alone or in combination, do[es] not teach or suggest a composition comprising a cell **nucleus** comprising a plurality of polynucleotide molecules and an insertional

enzyme complex comprising an insertion enzyme and an insert element... [or] the composition further comprising open chromatin regions.” EX1007, 224.

Petitioner now asserts that “the primary inventor” “put to rest” “any suggestion that the claimed invention of the ’357 Patent is novel or inventive” in a tweet. Pet.4. Not so. Instead, that tweet confirms the technical advancements in the Challenged Claims. Jason Buenrostro tweeted: “ATAC-seq is so easy to do that anyone can do it!” Pet.5. Prior to ATAC-seq, “[e]pigenomic studies of chromatin accessibility ha[d] yielded tremendous biological insights, but [were] limited in application by their *complex workflows* and *large cell number requirements*.” EX1001, 33:35-38. The innovative ATAC-seq method was a paradigm shifting technique that allowed researchers to quickly and simply analyze the epigenome of samples of any size. As an example, DNase-seq, is *44-steps*, requires *50 million cells* and *3 days* (two overnight incubations) to get results. EX1001, Fig.1B, 30:4-19. The compositions of the Challenged Claims are formed when the method referred to as “ATAC-seq” is practiced, a method of analyzing chromatin that, in comparison, can be practiced on as little as a *one-cell* sample in *two steps in less than a day*. *Id.* As Buenrostro confirmed, the novelty of the method is its simplicity and the possibilities it unlocked: “ATAC-seq is so easy... anyone can do it.” EX1029.

III. Petitioner's References

A. Grunenwald (EX1003)

Petitioner's central Grunenwald reference, U.S. Patent Application 2010/0120098, titled "Transposon End Compositions and Methods for Modifying Nucleic Acids," discloses methods, compositions, and kits for using a transposase and a transposon end to generate fragmented DNA for analysis. EX1003, 1 (Abstract). Grunenwald discloses a method for creating libraries of tagged DNA fragments for use in next-generation sequencing. EX1003, ¶¶11, 16.

As discussed above, Grunenwald was *cited to the Office* during the prosecution leading to '357 and *as a basis of rejection in the '357 itself*, and was also *repeatedly cited* and, indeed, *incorporated by reference into the specification of '357*. See, e.g., EX1001, 13:26-33 ('357 citing and incorporating "US20100120098" by reference (along with another publication) as describing this prior art system that "fragment[s] and add[s] adaptors to the polynucleotides"), 14:38-44 (cited (along with other art) as disclosing "method[] for tagmenting *isolated* genomic DNA"). But the Challenged Claims require, *inter alia*, a composition comprising a permeabilized cell nucleus with polynucleotides and an insertional enzyme complex within the intact nucleus. EX1001, cl.1. Dependent claims 2, 16, and 22 explicitly state that the insertional enzyme complex must bind to one of the open chromatin regions or that the tagged nucleic acids must be

derived from the open chromatin region. EX1001, cls. 2, 16, 22. '357 explains that it is used in performing methods which aim to avoid “perturbing *the in vivo context* and *modulating the epigenetic state* [of the cell] in unknown ways.” E.g., EX1001, cl.1; 1:43-46 (discussing one of “three major ways” existing protocols were “problematic”). In contrast, Grunenwald *does not mention chromatin at all or using its enzyme inside a nucleus*, and Grunenwald’s disclosures of results, methods, and data, are focused on *in vitro* transposition for fragmenting and acquiring the relevant *target DNA, which is not chromatin*, and *nowhere mentions using its enzyme inside an intact nucleus or permeabilizing the cell nucleus at all*. EX1003, ¶161; see, e.g., EX1001, 6:36-37 (contrasting “chromatin” with “naked genomic DNA”), 17:22-24 (contrasting “optional[] packag[ing] in the form of chromatin” with “genomic DNA” more generally); EX1007, 156.

Grunenwald states that “[a]n important step in embodiments of the method of the present invention is the use of an *in vitro* transposition reaction to fragment and tag the *target DNA* fragments. The *in vitro* transposition reaction requires a transposase...” EX1003, ¶92. Grunenwald further defines “transposase” to mean “an enzyme that is capable of forming a functional complex... and catalyzing insertion or transposition of the transposon end-containing composition into the double-stranded target DNA with which it is incubated in an *in vitro* transposition

reaction.” EX1003, ¶93. Even to the extent Grunenwald briefly mentions *in vivo* transposition, it does not address any transposition of chromosomal DNA *of the nucleus of a eukaryotic cell* (the only cellular location where chromatin exists) or using an insertional enzyme complex within an intact nucleus. EX1003, ¶157; EX1041, 1.

B. Okino (EX1004)

Okino is an international patent publication, WO 2010/065266, titled “Chromatin Structure Detection.” EX1004, 1. Petitioner cites Okino as a secondary reference, relying on it (just as the Examiner did with Jouvenot during prosecution) in attempting to show disclosure of permeabilizing the nucleus of a cell. Pet.25; EX1004, Fig.2, ¶44. Petitioner identifies NP40 and Tween detergents in Okino in attempt to show permeabilizing the nucleus, but Okino describes these detergents as, *e.g.*, “disrupting the *cell* membrane,” not permeabilizing the *nuclear* membrane. Pet.26 (citing EX1004 at [0012]). Indeed, Okino refers to permeabilization of the cell but never expressly states the *nucleus* is permeabilized, and Petitioner does not assert inherency. EX1004, Fig.2, ¶44; Pet.24-27.

C. Saleh (EX1005)

Saleh is titled “An efficient chromatin immunoprecipitation (*ChIP*) protocol for studying histone modifications in *Arabidopsis* plants.” EX1005, 1. Petitioner

relies on Saleh for disclosures allegedly related to claim 29 and isolating nuclei.

Pet.57-59. As its title reflects, Saleh is focused on a previously-existing protocol significantly different from ATAC-seq, termed “ChIP-Seq”—a prior art

immunoprecipitation method distinguished in the ’357. *E.g.*, EX1001, 14:63-65.

Unlike the ’357, immunoprecipitation (as the Office found in the Notice of Allowance in a related application) “involves the use of an insertional complex that comprises an antibody specific to a protein that is part of the chromatin.” EX2001, 437-438; EX1005, 3 (“Immunoprecipitate the DNA-protein complex using specific antibodies.”). And Saleh relies on “sonication” to “shear the DNA” which is the use of ultrasound to fragment DNA, as opposed to the ’357’s use of tagmentation. EX1005, 3; EX1001, 1:59-67.

D. Adey (EX1009)

Adey is an article titled “Rapid, low-input, low-bias construction of shotgun fragment libraries by high-density *in vitro* transposition.” EX1009, 1. Petitioner relies on Adey for disclosures allegedly related to claim 16 and a second nucleic acid insert element. Pet.62-64. Unlike ’357, Adey discloses an *in vitro* method of fragmenting isolated target DNA (as opposed to chromatin of a genome region). EX1009, 11-12 (“DNA was then isolated...”).

E. Song (EX1060)⁴

Song is an article titled “DNase-seq: A High-Resolution Technique for Mapping Active Gene Regulatory Elements across the Genome from Mammalian Cells.” Petitioner cites Song as a secondary reference, relying on it for lysing cell membranes to isolate nuclei using the IGEPAL detergent. Pet.20-21, 57-62. Song’s DNase-seq method is a technique distinguished in the ’357. EX1001, Fig.1B, 30:4-19.

IV. Claim Construction

No terms require construction for considering institution. *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999). If a proceeding is instituted, 10x reserves the right to address the construction of certain terms in view of the specification and the embodiments described therein. For the purpose

⁴ Petitioner refers to “Song” in its introduction of the reference, but then confusingly cites to EX1004, which is *Okino*. Pet.20; EX1004. This is confusing, lacks the required particularity (*see infra*, §V.B), and forces PO into the role of truffle hunter, rooting around for Petitioner’s possible meaning. *See U.S. v. Dunkel*, 927 F.2d 955, 956 (7th Cir. 1991) (“Judges are not like pigs, hunting for truffles buried in briefs.”). PO will assume Petitioner intended to cite EX1060 in this section. *Infra*, §V.B.

of this POPR, 10x has assumed the constructions explicitly set forth in the Petition.
Pet.21.

V. Grounds 1-3: Petitioner’s Obviousness Analyses Have Threshold Failures

All of Petitioner’s Grounds share two fundamental failures. First, Petitioner has failed even to assert, let alone prove, that any of its references are analogous art *to the challenged patent* as required for obviousness. Second, the Petition contains multiple glaring particularity failures. While a single failure might not suffice to doom a petition, the combination of failures here forces PO and the Board to guess at, *inter alia*,⁵ what embodiments from its references Petitioner intends to rely on from its asserted combinations (or how Petitioner is relying on unrelated embodiments), and how Saleh and Song (cited by Petitioner for the same limitation) are argued to be combined with Grunenwald and Okino. Institution denial is required for each of these reasons.

A. Petitioner Fails to Assert—Let Alone Prove—Its References are Analogous Art to the ’357

Nowhere does Petitioner assert—let alone attempt to provide analysis to establish—that any of its references named in its grounds (Grunenwald, Okino,

⁵ As noted, the Petition is unclear even as to what exhibits Petitioner intends to cite. *See* n.4; *infra* §V.B & n.6.

Saleh, Song, and Adey) are analogous art *to* '357; instead, Petitioner simply suggests they are analogous *to its cited Grunenwald reference*. Pet.27-28, 59-61, 64-65. But a petitioner ***cannot meet its burden*** when it “argue[s] that [the prior art reference] is analogous to another prior art reference *and not the challenged patent*.” *Sanofi-Aventis*, 66 F.4th at 1374. “[A] patent challenger ***must compare the reference to the challenged patent***.” *Id.* Petitioner failed to perform this required analogous art analysis by failing to address whether its relied-upon art is analogous *to the challenged* '357; Petitioner only asserts that Okino, Saleh, Song, and Adey (Petitioner’s secondary obviousness references), are analogous *to Grunenwald* (its primary obviousness reference). Pet. 27-28, 59-61, 64-65. Thus, because Petitioner’s Grounds 1-3 rely entirely on obviousness, and Petitioner was therefore ***required*** but ***failed*** to establish that its obviousness art is analogous to the challenged '357 as a threshold issue, Grounds 1-3 must each be rejected as Petitioner cannot meet its burden to establish obviousness as a matter of law. *Sanofi-Aventis*, 66 F.4th at 1380.

B. Grounds 1-3 Lack Particularity

Petitions must identify “with particularity, each claim challenged, the grounds on which the challenge to each claim is based, and the evidence that supports the grounds for the challenge to each claim.” §312(a)(3). Grounds 1-3 fail to meet this requirement.

First, Petitioner’s repeated cites (or mis-cites) to its “Song” reference are confusing and disadvantage PO. In its Exhibit List, the Petition defines Song as EX1060. Pet.xv. But in the section describing Song, the Petition instead cites EX1004 (*Okino*) and EX1051⁶ (*Naumann*). Pet.20-21. While this seems at first to be a simple mistake, when the Petition discusses *Song* in Ground 1 (Pet.23), it relies on its expert (EX1002, ¶143) who cites Song (EX1060), but then the Petition immediately argues instead that *Okino*’s purported disclosure of a permeabilized cell nucleus renders the “permeabilized cell nucleus” limitation obvious. Pet.24-25. And in Ground 2 Petitioner cites to *both* EX1060 (Song) and EX1004 (Okino) as support for assertions relating to Song. Pet.58-59. Thus, it appears Petitioner’s reliance on Okino when discussing Song is *intentional*, but Petitioner does not explain how Okino relates to Song or supports its various assertions, and—even in grounds without Ground 2’s improper “and/or Song”—PO is unable to discern when or what Petitioner may be arguing reliance on Song and Okino together, as opposed to one or the other. *See Lyft, Inc. v. Ikorongo Tech. LLC*, IPR2021-00423,

⁶ Indeed, even the cite to EX1051 is incomprehensible. Pet.21. The cite is to “EX1051.040,” but EX1051 is only eight pages (not 40 or more), and the native pagination of EX1051 begins at 233. It is impossible to decipher what Petitioner intended to cite.

Pap.10, 18-19 (July 26, 2021) (“As such, we again decline to ‘play archaeologist with the record’ to attempt to decipher the answer here for each of the many citations to Exhibit 1007” as to whether the citations are to the exhibit as filed or to the provisional application when filed.).

Second, Petitioner relies on various, disconnected Grunenwald embodiments without acknowledging it is doing so and without explaining (or providing the mandatory obviousness analysis to show) how the disclosures would work together or why POSITA would have been motivated to combine the disparate teachings.⁷ *In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017) (obviousness requirements apply when combining embodiments from a single reference); *Amazon.com, Inc. v. AlmondNet, Inc.*, IPR2022-01455, Pap.12, 17-18 (Apr. 6,

⁷ Petitioner also grossly exaggerates, or even misstates portions of Grunenwald it cites. For example, Petitioner asserts “Grunenwald teaches that the purpose of its method includes interrogating ‘whole’ genomes of such organisms.” Pet.50 (citing EX1003, ¶15). Paragraph 15 says nothing of the sort. EX1003, ¶15. It only says the art needs “improved methods for generating libraries of DNA fragments... including amplification of whole or partial genomes from one organism....” EX1003, ¶15. This does not state, or even imply, that the purpose of Grunenwald is to “interrogat[e] ‘whole’ genomes.” Pet.50.

2023) (denying institution where petitioner failed to show why or how multiple distinct embodiments from its first obviousness reference would be combined to meet a limitation); *Lumenis BE Ltd. v. BTL Healthcare Techs., A.S.*, IPR2021-01280, Pap.8, 20-22 (Mar. 9, 2022) (same); *John Crane, Inc. v. Finalrod IP, LLC*, IPR2016-01827, Pap.6, 13-14 (Jan. 31, 2017) (denying institution and stating it is petitioner’s burden to explain “how and why specific teachings of the references would have been combined.”). For example, in claim 1 the Petition points to Grunenwald’s so-called “*in vivo* tagmentation method” (Pet.30) but *also* relies on Grunenwald’s Paragraph 161 (Pet.33), which states “[a]ll of the embodiments of the methods of the present invention disclosed herein use an *in vitro transposition reaction*....” EX1003, ¶¶157, 161. These appear, on their face, to be entirely different embodiments, but Petitioner completely ignores this and provides none of the analysis that would be required to combine them. As another example, in claim 7 (Pet.40-41) Petitioner focuses on Grunenwald’s teaching of “the use of a *Mu* transposase” (Pet.41), but then for claim 8 (which depends from claim 7) Petitioner relies on the “*Tn5* transposase” (Pet.42). Again, there is no explanation for this sudden switch. *Unified Patents Inc. v. GE Video Compression, LLC*, IPR2019-00726, Pap.7, 22-23 (Aug. 6, 2019) (“[T]he Petition does not differentiate between the different embodiments disclosed in Howard nor does it provide any reason to combine the two.”); *Markforged Inc. v. Continuous*

Composites, Inc., IPR2022-01220, Pap.8, 21-22 (Jan. 11, 2023) (“We agree with Patent Owner that Petitioner's reliance on two disparate embodiments... falls short of establishing a reasonable likelihood that those claims would have been obvious.”).

Third, the Petition’s Ground 2 is stated as “The Combination of Grunenwald, Okino, And Saleh And/Or Song.” Pet.57. At minimum, this appears to be invoking three different grounds, all of which must be addressed by PO. For the two grounds that appear to rely on Saleh or Song individually, Petitioner does not adequately explain how the grounds *differ* despite the two references being different on their faces: Saleh is a “ChIP” protocol (EX1005, 1) and Song is a “DNase-seq” protocol (EX1060, 1), but the Petition simply lumps them together without discussion. Pet.59-62. And for the apparent combination relying on both Saleh *and* Song, Petitioner points to *both* references for “routine methods of nucleus isolation” (Pet.60-61) but without explaining how these two different methods would be combined, for the same limitation, with Grunenwald and Okino. Pet.58-62; *ADT LLC v. Vivint, Inc.*, IPR2022-00634, Pap.7, 13-15 (Oct. 4, 2022) (denying institution where one of petitioner’s grounds lacked particularity and petitioner failed to explain the interplay between its two references relied on for the same limitations noting, if IPR were instituted, lack of particularity would prejudice owner); *Elk Eng’g Sdn. Bhd. v. Wilco Marsh Buggies & Draglines, Inc.*,

IPR2020-00344, Pap.12, 17-22 (Mar. 4, 2021) (denying rehearing where petitioner’s four grounds (of 20) lacked particularity and “infected the entire” petition); §312(a)(3).

Given the totality of these failures, instituting trial would impose an improper burden and a clear denial of due process on 10x, which would be forced to guess at Petitioner’s arguments and support, and defend against unexplained Grounds and permutations Petitioner could later attempt to bend one way or the other as trial proceeds: as 10x defeats one argument, Petitioner will certainly claim to have made another. *ADT*, IPR2022-00634, Pap.7, 13-15; *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 296 (2016) (Alito J., concurring in part) (“If a petition fails to state its challenge with particularity... the patent owner is forced to shoot into the dark. The potential for unfairness is obvious.”).

VI. Grounds 1-3: Petitioner’s Analysis Is Legally Deficient

Petitioner’s Ground 1 asserts obviousness of claims 1-28, and 30 over Grunenwald in view of Okino. Pet.22. But Petitioner fails to show any of the four independent claims covered in Ground 1 (on which Grounds 2 and 3 rely), claims 1-2, 16, and 22, are obvious. *First*, each claim requires there to be a permeabilized cell nucleus, and Petitioner’s obviousness combinations relies solely on Okino for this limitation. Pet.24-31, 37, 46, 53. But Petitioner fails to show Okino even discloses a permeabilized cell nucleus, let alone (as Petitioner argues)

permeabilizing a cell nucleus with nonionic *disrupting* agents NP40 or Tween 20, which Okino expressly contrasts with *permeabilizing* agents. **Second**, Petitioner repeatedly relies on inherency to fill gaps in its art, but fails to make the required showing that these limitations are *necessarily* present. **Third**, with respect to independent claims 2, 16, and 22, Petitioner fails to show that Grunenwald discloses an insertional enzyme complex “bound to one of said open chromatin regions.” **Fourth**, and finally, Petitioner’s motivation to combine parrots the Examiner’s asserted motivation to combine Grunenwald and Jouvenot during prosecution, and fails for (at least) the same reason argued by Applicant in prosecution: Petitioner fails to show there was a known problem with Grunenwald’s method and therefore no motivation to modify Grunenwald in the manner Petitioner suggests.

A. Petitioner Fails To Show Okino Discloses A Permeabilized Cell Nucleus (All Claims)

Petitioner’s grounds are premised on Okino disclosing a permeabilized cell nucleus, as required by each independent claim. Pet.22, 37, 46, 53. But Petitioner fails to show Okino even *discloses* a permeabilized *cell nucleus*, let alone *permeabilizing* one with “NP40 or Tween detergents,” as Petitioner asserts as the basis for its obviousness arguments. Pet.26

Petitioner asserts ’357 does not specifically discuss details of permeabilizing the cell nucleus because POSITA would know how to do so. Pet.22. But

Petitioner fails to establish that Okino, the reference it chooses to rely on for permeabilization of the nuclear membrane, actually includes any such disclosure. Indeed, despite Okino's references to permeabilizing the *cell* (EX1004, Fig.2), Okino never describes permeabilizing the ***nuclear membrane*** or discloses that its enzyme enters the nuclear membrane in this way. Petitioner has not established any explicit disclosure in Okino of this limitation, nor has it even asserted, let alone established, implicit disclosure, let alone inherency. Pet.24-27. Petitioner's attempt to distract from Okino's lack of disclosure of permeabilizing a ***nuclear*** membrane by presenting arguments about lysing or permeabilizing *cell* membranes, ignoring the distinctions between a cell membrane and a nuclear membrane,⁸ and attempting to draw parallels between the '357 and Okino that do not exist, cannot meet Petitioner's burden.

Petitioner does not and cannot establish permeabilization of the nuclear membrane by showing lysis of the cellular membrane in the '357. Petitioner argues the '357 discloses lysing the cells (*i.e.*, cellular membranes), and jumps from that assertion to the conclusion that *any* manner of lysing cells would *also*

⁸ Petitioner ignores, *inter alia*, that the structure of the cell membrane (a lipid bilayer) is different from the structure of a nuclear membrane (a double lipid bilayer). EX2008, 34.

permeabilize the nuclear envelope. Pet.22-24. But Petitioner never identifies any *conditions* (e.g., the buffer and buffer concentration) that POSITA would have understood would cause both cell lysis and nuclear membrane permeabilization in the '357 that are *also* described in Okino.⁹ Pet.24-27. Indeed, while Petitioner points to an example of a “standard lysis protocol” using IGEPAL *in the '357*, Petitioner does not identify any parallel disclosures of the use of IGEPAL in Okino. Pet.22-27.

Even if Petitioner had established that the same conditions in Okino that *lyse* cell membranes also permeabilize nuclear membranes (a connection it has not provided sufficient proof to establish), Petitioner cannot point to disclosures in Okino of *permeabilizing* the cell membrane to establish permeabilization of the nuclear membrane. Pet.24-27. Petitioner points to quotes in Okino it alleges are about *permeabilizing* the *cell membrane* (Pet.24), but again never shows that any conditions in Okino that would cause cell membrane permeabilization would *also* cause nuclear membrane permeabilization. Pet.24-27. Thus, Petitioner has not shown how any alleged connection between *lysing* the cell membrane and permeabilizing its nuclear membrane would be relevant to the cited Okino disclosures of *permeabilizing* the cell membrane anyway. And, in any case, trying to establish permeabilization of nuclear membranes by pointing to the lysing of

⁹ And in any case, again, *Petitioner doesn't argue inherency* here.

cell membranes would require Petitioner to establish inherency, which Petitioner has not even alleged, let alone established. *ESET, LLC v. Finjan, Inc.*, IPR2017-01738, Pap.57, 37-39 (Jan. 24, 2019) (“To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference”).

Petitioner’s citation to Okino’s cartoon drawing of “Cell Permeabilization and Nuclease Digestion” also cannot meet its burden, as Petitioner points to no disclosure in Okino addressing *how* Okino’s enzyme enters the nucleus or establishing that it enters through permeabilization. *See* Pet.25 (citing EX1004, Fig.2). In fact, Petitioner asserts the “nuclease... ***can also enter the nucleus...***” Pet.25. But an assertion that something “can” happen is insufficient to demonstrate that it is disclosed. *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 960 (Fed. Cir. 2014) (affirming finding of no anticipation for failing to show application of bimatoprost to skin was inherently present in reference where the evidence only showed that “application of eyedrops containing bimatoprost can result in the promotion of eyelash hair” and that application of the eyedrops “may contact skin”) (emphases original); *Crown Operations Int’l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1377 (Fed. Cir. 2002) (“The mere fact that a certain thing may result from a given set of circumstances is not sufficient.”) (citing *Cont’l Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268–69 (Fed. Cir. 1991)). The Petition

does not allege inherency, and in any case never shows (nor could it) that the *only* way nuclease can enter the nucleus is through permeabilization. Thus, the *mere presence* of nuclease in a nucleus fails to carry Petitioner's burden. Petitioner's next sentence simply jumps to the conclusion that the "figure establishes... Okino permeabilizes the cell nucleus"—a logical leap that Petitioner fails to support with sufficient explanation. Pet.25-26.

Petitioner's identification of Okino's disclosures of NP40 and Tween 20 has the same shortcomings identified above, and only adds confusion to Petitioner's theory. Pet.26. Petitioner's discussion of NP40 and Tween 20 seems be intended to relate to a discussion Petitioner contends is about permeabilizing cell membranes. Pet.26 (quoting EX1004 at [0012] ("In some embodiments, the permeabilizing or disrupting step comprises disrupting *the cell membrane* with a nonionic detergent. In some embodiments, the nonionic detergent is selected from the group of NP40, Tween20 and Triton X-100.")). However, Petitioner's citations to NP40 and Tween20 in Okino describe the buffers as lysing (*i.e.*, "disrupting") cell membranes.¹⁰ In contrast, Petitioner's citations to the '357 describe these

¹⁰ Okino expressly contrasts "permeabilizing" a cell membrane with "disrupting" a cell membrane, and defines "disrupting" as "reducing the integrity of a cell membrane such that the cell's structure does not remain intact." EX1004, ¶¶34, 64

buffers as used in the '357 as permeabilizing the cell membrane. Pet.26 (citing EX1001, 3:24-26). Petitioner does not address whether its contention is that these buffers, *as used in Okino*, would lyse rather than permeabilize the cellular membrane or the nuclear membrane.¹¹

B. Petitioner's Many Inherency Arguments Fail

To fill many of the additional gaps in its prior art combination, Petitioner repeatedly argues limitations are “inherent” throughout Ground 1. Petitioner's inherency theories fail because Petitioner fails to present “persuasive technical reasoning to explain” that a limitation would *necessarily* be met. *See, e.g., Albaad Massuot Yitzhak, Ltd. v. Edgewell Pers. Care Brands, LLC*, IPR2017-00693, Pap.11, 9-10 (July 17, 2017). A conclusory assertion of inherency is not entitled to any weight. *Id.* Further, inherency may not be established by “*probabilities or possibilities.*” *See, e.g., Crown Operations.*, 289 F.3d at 1377; *see also Mylan*

(“The invention allows for analysis of chromatin structure by permeabilizing *or* disrupting cell membranes...”).

¹¹ Further, Petitioner points to EX1062 (“Ji”), *not* Okino, as disclosing *use conditions* for NP40, and its own parenthetical describes those conditions as “sufficient to cause cell lysis” (*not nucleus permeabilization*). Pet.26-27. But a review of Ji confirms it says *nothing* about permeabilizing a cell nucleus. EX1062.

Pharms. Inc. v. Merck Sharp & Dohme Corp., IPR2020-00040, Pap.91, 35-41

(May 7, 2021) (finding no inherency where the necessary salt “does not form ‘**every time**’” and explaining the “inherent result must inevitably result from the disclosed steps”); *ESET*, IPR2017-01738, Pap.57, 37-39 (finding no inherency where evidence was that limitation “**might**” have been present); *Pungkuk Wire Mfg. Co. v. Seong, Ki Chul*, IPR2016-00763, Pap.70, 8-10 (Aug. 16, 2017) (finding no inherency where evidence only established “it is **nearly** impossible” to practice claim without causing the necessary result); *Galderma Lab’ys, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App’x 838, 845-46 (Fed. Cir. 2020) (nonprecedential) (reversing anticipation where efficacy limitations were not inherent because art did not disclose the specific formulation and varying the factors in the disclosed formulations would lead to some formulations lacking the claimed efficacy limitations). “The mere fact that a certain thing **may** result from a given set of circumstances is not sufficient.” *Crown Operations*, 289 F.3d at 1377. Here, Petitioner’s conclusory assertions of inherency cannot meet its burden, and its expert does little more than parrot the Petition.

For **claim 1**, Petitioner’s apparent argument that “a plurality of polynucleotide molecules” is inherent (Pet.32 (“necessarily involve... a plurality of polynucleotide[s]”)) is flawed. Petitioner *admits* this would only be true in “**almost** all eukaryotic organisms” because **some** eukaryotic organisms have only a

single chromosome. Pet.32. Thus, on its face, Petitioner’s claim 1 argument is deficient as it is *not “necessarily” the case* any composition will have a plurality of polynucleotides as Petitioner freely concedes.¹²

For element G of **claim 2**, Petitioner argues it is inherent that the transposase will bind to chromatin. Pet.38 (Section X.A.2.d (arguing Grunenwald discloses chromatin))¹³; Pet.39 (Section X.A.2.g). Petitioner’s only purported support for

¹² Petitioner’s alternative theory is that, even if not inherent, there are a “plurality of polynucleotide molecules” because the single chromosome would be tagmented. Pet.32-33. But Petitioner did not construe this term, and fails to explain how *tagmenting one polynucleotide into fragments* satisfies that limitation (including because Petitioner confusingly cites only to its POSITA standard as support). Pet.29-31. And indeed, this claim language clearly require a plurality of polynucleotide molecules in the nucleus, not a single polynucleotide that is later broken up. *Compare, e.g.*, EX1001, cl.1 (“plurality of polynucleotide molecules”) *with* cl.16 (“plurality of tagged nucleic acid fragments”).

¹³ Petitioner fails to show Grunenwald applies its method to chromatin, a nucleus, or a eukaryotic cell *in vivo* (let alone one with a permeabilized cell nucleus). *Infra*, §VI.C. Petitioner’s Section X.A.2.g arguments simply *assume* this limitation is met, and thus also fail for this additional reason.

this inherency argument is its expert's Paragraph 208. Pet.39. But this expert, in turn, only states "it would have been known and well-established in the art that these types of transposases *preferentially* bind to open chromatin." EX1002, ¶208. This generalized assertion is, *inter alia*, insufficient to establish this binding will necessarily occur under the conditions in Petitioner's combination of Grunenwald and Okino. The expert's only citation here, EX1052, similarly fails to support the assertion that the *Mu* transposase will necessarily bind to open chromatin in the conditions of Grunenwald, let alone in conditions modified by the presence of Okino's nonionic detergents. EX1052, 1. Instead of attempting to address this, Petitioner just asserts it is so. Petitioner's analysis for **claims 16 and 22** relies on this same claim 2 argument, and thus fails for the same reasons. Pet.50 (citing Section IX.A.2.g for support); Pet.53 (citing X.A.2.g).

Finally, for **claim 22**, Petitioner also fails to show it is inherent that "a high-affinity macromolecular complex" will be formed. Pet.53-54. Rather than showing with "persuasive technical reasoning" that it will necessarily occur in Petitioner's cobbled-together assembly of bits from the prior art, Petitioner points to '357's specification. Pet.54. But Petitioner never explains how this passage from '357 demonstrates this complex would necessarily be formed with any use of a Tn5 transposase under the conditions presented in its prior art references. Petitioner does not (and cannot) show the same experimental conditions are used in

Grunenwald as in the '357, and Petitioner makes no other attempt to support its inherency argument. Pet.54. Petitioner's only purported support (other than the '357 itself) is two paragraphs from its expert's declaration (EX1002, ¶¶320-321), which *total three sentences*. Pet.54. Petitioner's expert asserts "it was a well-known property of the Tn5 transposase that it would remain 'tightly bound to the ends of the resulting fragment.'" EX1002, ¶¶320-321. But the expert's only cited basis for this conclusion is a single page from EX1059, which does not support the assertion that tagmentation with a Tn5 will necessarily result in a "high-affinity macromolecular complex" under any conditions. EX1059, 266. Indeed, that single cited page does not even identify what transposase is being used, and neither Petitioner nor its expert ever attempts to show that the conditions of use in EX1059 are the same as those disclosed in Grunenwald or its Grunenwald-Okino combination such that EX1059's conclusions would apply. Pet.54; EX1002, ¶¶320-321. Petitioner has thus failed here, as well.

C. Petitioner Fails To Show Grunenwald Discloses "the insertional enzyme complex is bound to one of said open chromatin regions" (Claims 2-30)

Element C of claim 2 (and, in turn, element G of claim 2 (Pet.37-38)) requires that the insertional enzyme complex binds chromatin *inside a nucleus with a permeabilized membrane*. The Petition argues that "Grunenwald discloses contacting a cell, and thus a cell nucleus, directly with an insertional enzyme

complex to accomplish tagmentation.” Pet.37 (citing EX1003, ¶157).¹⁴ Petitioner concludes that, “[b]ecause of this disclosure and the inherent nature of a cell nucleus, Grunenwald discloses [chromatin].” Pet.38. But Petitioner’s conclusory assertions fail to establish that Grunenwald discloses an “insertional enzyme complex” bound to “open chromatin,” let alone an insertional enzyme complex inside a permeabilized nucleus. Pet.37-39; *supra* 33-34. Indeed, open chromatin is located *inside* the nucleus, as Petitioner recognizes (Pet.37-38), and therefore the claim’s requirement that the insertional enzyme complex bind open chromatin reflects the requirement that it enter the nucleus. Pet.38. Petitioner’s challenges to independent claims 16 (Pet.50 (citing Section IX.A.2.g)) and 22 (Pet.53 (same))

¹⁴ Petitioner does not assert in this Petition that Grunenwald *inherently* discloses ***contacting chromatin with an insertional enzyme complex***. Pet.37-38. Petitioner only argues a “cell nucleus necessarily and inherently ***contains chromatin***.” *Id.* Pet.37-38. To the extent Petitioner is asserting all cells have chromatin, PO disagrees, as this is only true for eukaryotic cells, not all cells. EX2007, 4; Pet.37-38. PO reserves the right to respond to the extent Petitioner is permitted (it should not be) to shift to new theories after its Petition and argue, instead, Grunenwald inherently discloses contacting chromatin.

and the challenged dependent claims (3-15, 17-21 and 23-30) also fail for these reasons.

Grunenwald Paragraph 157, cited by Petitioner as the support for its conclusory assertion that Grunenwald teaches an insertional enzyme complex that contacts a nucleus and accomplishes tagmentation, ***does not mention a nucleus*** or ***“chromatin”*** (the complex of molecules including proteins and polynucleotides “as found in a nucleus of a eukaryotic cell” (EX1001, 12:61-63)). Paragraph 157 also does not state that any *in vivo* tagmentation is applied to a eukaryotic cell (the only cell with a nucleus or chromatin). EX1003, ¶157. Indeed, Petitioner points to no indication in that paragraph that an insertional enzyme complex contacts chromatin or anything else inside the nucleus.¹⁵ Inexplicably, Petitioner nevertheless concludes “Grunenwald discloses this limitation.” Pet.38.

Petitioner’s assertions are facially insufficient to carry its burden. *Salpeter v. ARP Wave, LLC*, IPR2019-01384, Pap.12, 16-17, 22 (Jan. 27, 2020) (denying institution and stating “[r]ejections on obviousness grounds cannot be sustained by mere

¹⁵ And while Petitioner does not even argue inherency, that paragraph also contains no indication that *in vivo* tagmentation to a eukaryotic cell necessarily results in the nucleus being contacted. EX1003, ¶157; EX2007, 4.

conclusory statements”) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

Petitioner’s conclusory assertion is also not supported by the cited paragraph of its expert’s declaration. Pet.37-38 (citing only ¶195 of EX1002). The Petition’s only cite to its expert for the limitation “chromatin comprising genomic DNA and a plurality of DNA binding proteins” refers to an assertion from its expert that “chromatin is the endogenous from of DNA.” Pet.37 (citing EX1002, ¶195). That paragraph never refers to Grunenwald, or explains how Grunenwald’s generic reference to an *in vivo* embodiment supposedly discloses chromatin or a nucleus. EX1002, ¶195.¹⁶ And even if, *arguendo*, the expert’s assertion supported

¹⁶ To the extent, *arguendo*, Petitioner intended to cite Paragraphs 196-200 of Dr. Cooper’s declaration rather than 195 (and to the extent, *arguendo*, **uncited** Paragraphs 196-200 are even considered by the Board (the Petition provides no basis for doing so)), Petitioner still fails to meet its burden as its expert’s analysis is deficient. *Cisco Sys., Inc. v. C-Cation Techs., LLC*, IPR2014-00454, Pap.12, 9-10 (Aug. 29, 2014) (informative); *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Pap.9, 15-16 (Aug. 24, 2022). Petitioner’s expert attempts to twist a *definition* of “target DNA” into an express disclosure of Grunenwald performing its method on chromatin (EX1002, ¶¶196-200), but points to no disclosure of Grunenwald’s

Petitioner’s contention (it doesn’t), it should be given no weight: it is conclusory and lacks the required disclosure of underlying factual support and reasoning for the opinions. *Xerox*, IPR2022-00624, Pap.9, 15-16 (denying institution and according petitioner’s expert “little weight” where the expert’s declaration was conclusory and failed to “cite to any additional supporting evidence or provide any technical reasoning to support his statement”); *Motorola Mobility LLC v. Maxell, Ltd.*, IPR2023-00110, Pap.7, 34-35 (June 15, 2023) (same).

method being used on “chromosomal DNA” in a cell—let alone on a *eukaryotic* cell (which is the only kind of cell that would have chromatin) or chromatin specifically. EX1036, 2; EX2007, 4-5. Further, Petitioner’s expert fails to explain why or how POSITA would have understood “chromosomal DNA” to mean ***chromatin*** as opposed to naked DNA. EX1002, ¶¶196-200. Lastly, while Petitioner’s expert mentions inherency, the Petition does not (Pet.37-38), and the expert’s conclusory assertion of inherency fails. EX1002, ¶200; see *Universal Imaging Indus., LLC v. Lexmark Int’l, Inc.*, IPR2019-01381, Pap.7, 19-20 (Feb. 3, 2020) (refusing to consider expert declarant’s inherency testimony where that theory was not argued in the petition, stating “[i]f Petitioner intends to rely on inherency, the Petition must include an argument regarding inherency.”).

D. Petitioner Fails To Show POSITA Would Be Motivated To Combine Grunenwald And Okino (All Claims)

For each independent claim argued in Ground 1 (which are relied upon for the dependent Challenged Claims including those in Grounds 2 and 3¹⁷), Petitioner relies on the same motivation to combine argument from claim 1. Pet.27-31, 46, 53, 59-62, 65. Petitioner suggests there are “several reasons [POSITA] would have been motivated to combine Okino’s permeabilized cell nuclei with Grunenwald,” but then argues just one: that POSITA would recognize Okino’s permeabilization is an alternative to Grunenwald’s, and therefore using one over the other is a mere “design choice.” Pet.27-31; *Thor Indus., Inc. v. Grand Design RV, LLC*, IPR2022-00411, Pap.9, 41-44 (July 14, 2022) (denying institution where petitioner asserted using a “truss or beam” was a mere design choice because this failed to show a benefit, and petitioner’s experts parroted the petition and failed to show any benefit in the substitution); *Current Lighting Sols., LLC v. ALSI Holdings, LLC*, IPR2023-00125, Pap.12, 18-20 (May 3, 2023) (denying institution where petitioner asserted it “would have been an obvious design choice” to use retrofit prior art with a LED

¹⁷ Ground 3 adds Adey only for the disclosure of “a first sequencing adapter and second sequencing adapter.” Pet.62. It does not purport to fill any gaps of Ground 1 identified in Sections V-VI.

lighting system without pointing to any “objective evidence sufficient to show that the proposed modification would provide any particular benefit”). This fails.

Petitioner argues that “Grunenwald teaches that just about any source of DNA may be used in its tagmentation method” and that Grunenwald teaches its “method can be carried out on ‘chromosomal DNA’... by introducing the transposase directly into a cell” via electroporation. Pet.27-28. Petitioner then concludes POSITA would have “considered other alternatives to [electroporation] to gain access and/or improve access to the genetic material in the cell nucleus” and would have looked to Okino. Pet.29.

To begin, Petitioner has not established that Grunenwald discloses contacting a cell nucleus and that Okino discloses permeabilizing a cell nucleus, as discussed above. *Supra*, §VI.A-B. But even setting those failures aside, Petitioner never identifies a problem POSITA would have sought to solve in Grunenwald’s electroporation method, which Petitioner itself argues already allowed POSITA “to gain access,” and additionally fails to explain how Okino’s nonionic detergents would have “improve[d] access” such that POSITA would have looked to its disclosures. Pet.29; *In re Schweickert*, 676 F. App’x 988, 995 (Fed. Cir. 2017) (reversing Board’s obviousness determination where proposed modification of prior art is “unnecessary” to prior art system that “already” performs function of proposed additional feature and “would do little more than add unwanted cost and

complexity to the system”); *Thor*, IPR2022-00411, Pap.9 41-44; *Current Lighting*, IPR2023-00125, Pap.12, 18-19. As the Applicant argued in prosecution (EX1007, 200) and the Examiner concluded was persuasive in withdrawing its rejection based on Grunenwald in view of Jouvenot and allowing ’357’s claims (EX1007, 152-158, 224), there was no known problem in Grunenwald, and thus no motivation to modify Grunenwald by adding NP40 or Tween 20 to permeabilize the cell nucleus and analyze the chromatin within. *Id.* Even with this failure of the same obviousness rationale in hand (*see* EX1007), Petitioner failed to address it, and its Grounds all fail.

VII. Grounds 2-3: Petitioner’s Other Obviousness Analyses Are Flawed And Cannot Support A Finding Of Obviousness

Petitioner cannot meet its burden as to Grounds 2-3 for the same reasons Petitioner cannot meet its burden for Ground 1 in addition to the issues identified below.¹⁸ *Supra*, §V.

A. Petitioner’s Motivation To Combine And Reasonable Expectation Of Success Analyses Are Conclusory

Petitioner’s “arguments” that POSITA would be motivated to combine its various references, and have a reasonable expectation success in doing so, are entirely conclusory for each of its Grounds 2-3, and therefore fail. *Salpeter*,

¹⁸ *Supra* n.17.

IPR2019-01384, Pap.12, 16-17; *Health Care Logistics, Inc. v. Kit Check, Inc.*, IPR2019-00385, Pap.7, 14-15 (June 3, 2019) (denying institution and noting “[i]n the absence of a persuasive rationale supporting the asserted combination of prior art, it is insufficient for Petitioner to merely use [the claims] as templates to piece together the teachings of the prior art so that the claims are rendered obvious.”); *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016) (“To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements. The petitioner must instead articulate specific reasoning based on evidence of record, to support the legal conclusion of obviousness.”).

For **Ground 2**, for example, Petitioner identifies no problem with its purported combination of Grunenwald and Okino requiring further improvement, and identifies no benefit that “Saleh and/or Song” would provide to Grunenwald’s tagmentation method or its Grunenwald-Okino combination. Pet.60-61. Petitioner makes the conclusory assertion that “nuclei isolation provides” “quality improvements.”¹⁹ But Petitioner does not establish POSITA would have sought

¹⁹ Petitioner elsewhere recognizes Saleh and Song apply different methods of chromatin analysis. Pet.57-60. Saleh is focused on ChIP-seq, and Song is focused on DNase-seq, both of which are prior art methods distinguished in the ’357.

EX1001, Fig.1B, 30:4-19.

“quality improvements” for Grunenwald (or what sort of “quality” improvements they would have been), or whether or how “nuclei isolation” would improve the Grunenwald’s “quality.” Pet.60. Moreover, Petitioner entirely ignores that, according to Petitioner, Okino seemingly isolates the nuclei via use of its lysis agents, which lyse the cell membrane. Pet.26 (“While the ’357 Patent includes the IGEPAL detergent for cell lysis in its working example... it was well known that other detergents, such as the NP40 detergent identified in both Okino and the ’357 Patent, also work to disrupt membranes.”). To the extent the nucleus is not also lysed in Okino (as Petitioner argues), it is isolated. Petitioner does not explain, then, what Saleh and/or Song add to the combination. Pet.60-61. Thus, Petitioner’s conclusory analysis failed to establish the foundation on which its purported motivation to combine lies.

For **Ground 3**, Petitioner merely argues that “POSA seeking to prepare chromatin for sequencing would have found it obvious to try using the methods taught in Adey, particularly the use of the Nextera™ kit, for the tagmentation methods taught in Grunenwald.” Pet.64. But Petitioner does not identify what benefit the Nextera™ kit would provide, or any other reason POSITA would have been motivated to implement Adey’s tagmentation method with Grunenwald. Pet.64-65. Petitioner’s argument is no more than POSITA *could* have used Adey’s Nextera™ kit with Grunenwald, but that does not establish POSITA *would* have

been motivated to do so. *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir. 2020) (“The obviousness inquiry does not merely ask whether a skilled artisan *could* combine the references, but instead asks whether ‘they *would have been motivated* to do so.’”); *Thor*, IPR2022-00411, Pap.9 41-44; *Current Lighting*, IPR2023-00125, Pap.12, 18-19. Further, Adey purports to be about “*in vitro* transposition” (EX1009, 1), and Petitioner has not addressed why or how POSITA would combine the alleged *in vivo* disclosures of Grunenwald with an *in vitro* reference like Adey.

In sum, Petitioner failed to meet its burden with respect to motivation to combine and reasonable expectation of success for any of its obviousness grounds.

VIII. Institution Should Be Denied Under 35 U.S.C. §325(d)

This Petition, which simply rehashes art that was before the Examiner, along with secondary references merely cumulative of that art, without showing Examiner error is precisely the sort of wasteful do-over the *Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH* (IPR2019-01469, Pap.6, 8-9 (Feb. 13, 2020) (precedential) (“AB”)) framework was intended to prevent. Both parts of the *AB* framework point to denial.

As to *AB* part one, Petitioner’s central reference, **Grunenwald**—the primary reference for Ground 1, and on which all of Petitioner’s other Grounds depend—was *the basis of a rejection during ’357’s prosecution* (and listed on ’357’s face)

(EX1001, 1; EX1007, 152-157; Pet.66), and it was also *explicitly cited twice in the as-filed specification that the Office examined in related applications*—including in a passage affirmatively *incorporating Grunenwald by reference* for its teachings of a prior art system that, *inter alia*, “fragment[s] and add[s] adaptors to the polynucleotides.” EX1001, 13:26-33, 14:38-44; EX2001, 29 (17:16-20), 25-26 (18:33-19:2). Additionally, Grunenwald was introduced by applicant in the first IDS filed in the first non-provisional application in ’357’s family (before the same Examiner as ’357) (EX2001, 295); and the patent into which Grunenwald matured, U.S. Patent 9,080,211, was *also* of record during both ’357’s prosecution and prosecution of prior related applications. EX1001, 1; EX1007, 10-11; EX2001, 401; EX2003; *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Pap.8, 22-23 (Dec. 15, 2017) (precedential as to §III.C.5, first paragraph) (“*Becton*”); *see Motorola Mobility LLC v. Maxell, Ltd.*, IPR2022-01287, Pap.11, 16 n.8 (Feb. 2, 2023). Of Petitioner’s four other secondary²⁰ references, Petitioner does not dispute three (Okino, Adey, and Song) were before the Examiner—and Petitioner fails to show that the last one (Saleh) is anything other than cumulative of art that was. Pet.66 (“Applicant identified... Okino... Saleh was not considered”); EX1001, 1-2 (identifying Adey and Song). Indeed, Petitioner’s

²⁰ *See supra*, §VI.C.

failure to conduct *any* analysis of whether its art was cumulative is, by itself, fatal under *AB* part one.

And as to *AB* part two, Petitioner further fails to show *any* Examiner error, let alone a material one. Petitioner's only allegation is that the Examiner erred "by not considering the relevant teachings in Grunenwald and Okino, or in Grunenwald and Okino in combination with Saleh," arguing the Examiner "did not discuss or cite any passage or disclosure of Okino" and did not discuss Grunenwald's single *in vivo* reference. Pet.67. Petitioner then goes on to argue that "the fact that these references 'w[ere] not the basis of a rejection weighs strongly against exercising [the Board's] discretion to deny institution.'" Pet.67. This statement, even in the kindest light, approaches absurdity: Grunenwald was the subject of a detailed obviousness rejection in combination with Jouvenot, which is wholly cumulative of Okino. EX1007, 151-158. Petitioner's argument is essentially a complaint that the Examiner failed to discuss explicitly a single specific sentence of Grunenwald in the rejections she made. But Petitioner entirely fails to show how that *in vivo* embodiment was overlooked (given the Examiner's thorough analysis) or how it would expressly disclose the permeabilized cell nucleus the Examiner found to be missing. Pet.67-68. Thus, Petitioner fails to assert, let alone explain, why the Examiner's conclusion as to patentability would have differed based on these

additional cumulative references²¹ and arguments. Pet.67-68; *Becton*, 22-23; see *Motorola*, IPR2022-01287, Pap.11, 16 n.8.

Revisiting the same or substantially the same previously-considered art and arguments already overcome during prosecution without any showing of material error—simply because Petitioner wishes for a different outcome—is a waste of the Board’s limited resources and unfairly burdens 10x.

A. Advanced Bionics Part One Favors Denial

AB part one considers whether the same or “substantially the same” art or arguments “previously were presented to the Office.” *AB*, 8. The *Becton* Factors relevant to *AB*’s part one inquiry include: “(a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination;” and “(d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art.” *AB*, 9 n.10, 10; see also *Becton*, 17-18.

Petitioner offers up only a three-sentence argument for *AB* part one in which it states Grunenwald and Okino were identified and Grunenwald was meaningfully

²¹ Again, Petitioner argues only Grunenwald, Okino, and Saleh to suggest part-two error. Pet.67-68.

analyzed during prosecution. Pet.66. Petitioner argues only that “Okino was not *cited* in any way during prosecution” and that “*Saleh* was not considered by the Examiner at all during prosecution.” *Id.* This is insufficient.

First, Petitioner’s Ground 1 is **Grunenwald** in view of **Okino**, and Grunenwald and Okino are also central to every *other* Ground urged by Petitioner. Pet.25. But Petitioner states that “Applicant identified Grunenwald and Okino” and that Grunenwald was meaningfully analyzed during prosecution. Pet.66. As noted above, while this is enough to confirm Grunenwald and Okino are “previously presented art” for purposes of *AB* part one, Petitioner’s description is also a wild understatement for Grunenwald: **Grunenwald** was affirmatively *incorporated by reference* into the ’357’s specification for its teachings of a system employing an “insertional enzyme complex,” including, *e.g.*, “an insertional enzyme and two adaptor molecules (the ‘transposon tags’) that are combined with polynucleotides to fragment and add adaptors to the polynucleotides.” EX1001, 13:26-33 (“Such a system is described in a variety of publications, including... US20100120098 [Grunenwald]... which [is] incorporated by reference herein”). Moreover, Grunenwald was before the same Examiner during the entire prosecution of ’357’s related applications. EX2001, 295. Additionally, Petitioner’s Grunenwald reference matured into U.S. Patent No.

9,080,211 (EX2003), which was *also* of record in the prosecution of the '357 and its relatives. EX1007, 10 (“9080211... Grunenwald”); EX2001, 401.

Petitioner states **Okino** was disclosed in prosecution. Pet.66. In any event, it is plainly cumulative of Jouvenot, which was affirmatively asserted by the Examiner. For example, Petitioner asserts Okino discloses “‘methods of permeabilizing’ a cell membrane that ‘will not disrupt the structure of the genomic DNA of the cell such that nucleosomal or chromatin structure is destroyed.’” Pet.24 (citing EX1004, ¶71). Petitioner also argues that “[c]ritically, the permeabilization agent used in Okino is a detergent, such as the common NP40 or Tween detergents.” Pet.26 (citing EX1004, ¶12). But (while Petitioner ignores this) the Examiner *found and asserted the same teachings* in Jouvenot, stating that “Jouvenot teaches that permeabilizing of the cell membrane occurs in such a way such that it will not disrupt the structure of the genomic DNA of the cell such that nucleosomal or chromatin structure is not destroyed [0055]. *Jouvenot teaches wherein such agents used to permeabilize the cells comprise of NP40, Tween 20 or Triton X-100.*” EX1007, 155-156. These are nearly verbatim statements of the disclosures argued by Petitioner, and there can be no dispute that Okino and Jouvenot are cumulative.

Nothing more is required under *AB* part one for Grunenwald or for Okino—or for **Song** and **Adey**, both of which Petitioner simply ignores. Petitioner does not

dispute both Song and Adey were also before the Examiner in '357's prosecution, or that Adey is discussed in '357's specification. EX1001, 28:32-38; Pet.66; EX1007, 187; EX2001, 388 (Adey also cited in IDS in '357's relative); *Agrinomix, LLC v. Mitchell Ellis Prods., Inc.*, IPR2017-00525, Pap.8, 10-11 (June 14, 2017) (denying institution under §325(d) where prior art reference was “discussed in the Specification” of challenged patent); *Keysight Techs., Inc. v. Centripetal Networks, Inc.*, IPR2022-01421, Pap.9, 9-10 (Mar. 22, 2023) (“*Advanced Bionics* makes clear that previously presented art includes art that was provided via an [IDS].”); *Ivantis, Inc. v. Sight Scis., Inc.*, IPR2022-01533, Pap.14, 13-14 (Mar. 27, 2023) (*AB* part one satisfied where an asserted reference was cumulative of a reference considered but not discussed during prosecution); *Becton*, 22-23; *Motorola*, IPR2022-01287, Pap. 11, 16 n.8.

Petitioner's only remaining argument for *AB* part one is that its final secondary reference, **Saleh**, “was not” in front of the Examiner “during prosecution.” Pet.66. To begin with, Saleh is relied on only as a secondary reference for Ground 2 (which covers just claim 29), and this is insufficient to stave off §325(d) denial. *Miltenyi Biomedicine GmbH v. The Trustees of the Univ. of Pa.*, IPR2022-00853, Pap.11, 45 (Oct. 11, 2022) (citing *Kayak Software Corp. v. IBM*, CBM2016-00075, Pap.16, 10 (Dec. 15, 2016) (informative) (finding reliance on new reference solely for “additional subject matter of certain dependent

claims[] is insufficient to persuade us that exercising our discretion under U.S.C. §325(d) is inappropriate.”)).

But Petitioner’s argument is also flawed: Saleh is at best *cumulative* of art that *was* before the Examiner. *See* §325(d) (encompassing “substantially the same” art). Petitioner tellingly *makes no argument* that Saleh is *not* cumulative of the art that was before the Examiner (Pet.66)—indeed, the Petition never uses the word “cumulative.” But this is a mandatory part of any §325(d) analysis, and Petitioner’s failure to include it is fatal to its *AB* part one argument. *See, e.g., Autel Intelligent Tech. Corp. v. Orange Elec. Co.*, IPR2021-01545, Pap.8, 17, 20-23, 27 (Apr. 8, 2022) (denying institution under §325(d) where Petitioner failed to “persuasively identify any specific, substantial difference between [petitioner’s reference] and the Third Reexamination’s prior art”); *see also Darfon Elecs. Corp. v. Shipman*, IPR2022-01008, Pap.11, 14 (Dec. 2, 2022) (denying institution under §325(d), noting “Petitioner does not address whether the proffered art is cumulative to or substantially the same as the art considered during prosecution.”); *Alarm.com, Inc. v. Vivint, Inc.*, IPR2022-00728, Pap.6, 20-22 (Nov. 1, 2022) (concluding art was cumulative, noting “Petitioner does not address the similarities between [references] applied during prosecution... and [the reference] relied upon in each of the asserted grounds”).

Moreover, had Petitioner bothered to provide this mandatory analysis, it would simply have confirmed Saleh *is* cumulative of art affirmatively argued in prior art rejections during prosecution of '357. Petitioner argues Saleh solely for purposes of claim 29, to supply purported teachings of isolating cell nuclei.

Pet.57-62. And ***Petitioner itself argues Song (which was undisputably before the Examiner) as an alternative disclosure to Saleh for this limitation***, effectively admitting that Song and Saleh are cumulative of each other. Pet.57-62, 66.

Thus, for each of Petitioner's cited references, the same or substantially the same ***art*** was already before the Office in connection with '357's prosecution.

Second, while Petitioner asserts its *arguments* here are new, it never explains why or how. Pet.66. Even if it had, this would be irrelevant and need not be reached by the Board: *AB* part one is met where art ***or*** arguments were previously presented. *Microsoft Corp. v. ThroughPuter, Inc.*, IPR2022-00757, Pap.10, 20 (Nov. 1, 2022). But additionally, as discussed above, these arguments are *not* new. The Examiner asserted that Grunenwald in view of Jouvenot rendered the '357 obvious. EX1007, 152-158. Petitioner makes the same argument but swaps out Jouvenot's disclosure of using NP40 or Tween 20 to permeabilize a cell nucleus for Okino's (alleged) cumulative discussion. *Supra*, 11-13.

Thus, *AB* part one is satisfied.

B. Advanced Bionics Part Two Favors Denial

AB part two considers whether a petitioner has demonstrated that the Office erred in a manner material to the challenged claims' patentability. *AB*, 8-9. *Becton* factors relevant to the part two inquiry include: (e) the record developed by the Office in previously reviewing the art or argument; (e) whether petitioner sufficiently pointed out how examiner erred in evaluating the art; and (f) the extent to which petitioner's additional evidence and facts warrant reconsideration of the prior art or arguments. *AB*, 9-10. "If a condition in the first part of the framework is satisfied and the petitioner fails to make a showing of material error, the Director generally will exercise discretion not to institute *inter partes* review." *Id.*, 8-9. "***If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability. At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.***" *Id.*, 9.

Petitioner asserts the Examiner "materially erred by not considering the relevant teachings of **Grunenwald and Okino, or in Grunenwald and Okino in combination with Saleh**,²²" including "by failing to acknowledge the teachings in Grunenwald regarding application of tagmentation to living cells *in vivo* that

²² Petitioner does not even argue error with respect to Saleh. Pet.67-68.

disclose transposition tagging on chromosomal target DNA and Okino that disclose permeabilization of the cell and nuclear membrane by the use of nonionic detergents, particularly NP40 and Tween20.” Pet.67-68. But this completely ignores the Examiner’s substantive rejection in ’357’s application based on Grunenwald and Jouvenot, of which Okino is cumulative (*supra*, §§II, VIII.A), as well as the Examiner’s previous rejection based on Fernandez in a related application.²³ EX2001, 380-381. It also ignores that ***Grunenwald, which Petitioner argues discloses these limitations (Pet.68), is incorporated by reference into the ’357. See Monolithic Power Sys., Inc. v. Volterra Semiconductor LLC***, IPR2020-01348, Pap.19, 11-13 (Mar. 4, 2021) (exercising §325(d) discretion and denying institution, noting it was “difficult to suggest that the Examiner merely ‘overlooked’” the reference that was incorporated by reference and discussed at multiple points in the challenged patent’s specification).

Petitioner makes similar complaints that the Examiner did not “acknowledge” the teachings of Okino that fail for the same reason, including because they were expressly discussed in connection with Jouvenot. *Supra*, §§II, VIII.A. Further, Petitioner does not even assert, let alone explain, how “acknowledging” the teachings of Saleh were material to patentability (and the

²³ It is also incorrect, as explained *supra*, §VI.C.

Petition effectively concedes they are cumulative of Song, which was before the Examiner). Pet.67-68, 57-59.

Petitioner's complaint that "the Examiner did not discuss or cite any passage or disclosure of" these two references (Pet.67) is nothing more than a complaint that the Examiner did not issue a rejection that Petitioner wishes she had. The caselaw confirms the Examiner's complained-of "silence" in this regard is not *AB* part two "error." *E.g., Microsoft Corp. v. AlmondNet, Inc.*, IPR2022-01319, Pap.9, 10-11 (Jan. 30, 2023). Far from showing error by the Examiner, this complaint that "the Examiner did not discuss the *in vivo* embodiment disclosed in Grunenwald" or Okino's permeabilization methods (Pet.67-68) is an attempt to transform the requirements of §325(d) into a standard requiring examiners to discuss every word of all potentially-relevant disclosures from every potentially relevant reference to avoid making a "material error," without even showing that the particular disclosure would have altered the Examiner's patentability determination. Pet.67-68. This is not the law. *AB*, 9 ("At bottom, this framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.").

1. The Examiner Made No Material Errors Of Fact

Grunenwald: Petitioner makes two equally unfounded assertions relating to Grunenwald. Petitioner first asserts this is a case where “the record of the Office’s previous considerations of the art is not well developed.” Pet.67. Nonsense.

Grunenwald was an explicit basis of rejection in the ’357 and, even according to Petitioner, was meaningfully analyzed by the Examiner. Pet.66. The Examiner argued invalidity based on many of the same Paragraphs of Grunenwald that Petitioner relies on—*e.g.*, Paragraphs 17 (Pet.16), 146 (Pet.17) 98 (Pet.34) 45 (Pet.39) 52, 94, and 98 (Pet.40); *see* EX1007, 152-157—and ***10x overcame that Grunenwald-based rejection*** in ’357’s prosecution. EX1007, 224-225. That rejection confirms the Examiner extensively reviewed Grunenwald and belies Petitioner’s imaginings that Paragraph 157 was somehow “overlooked.” EX1007, 154-155 (relying on surrounding paragraphs 146-147, 162, and 164). And indeed, Grunenwald was also called to the same Examiner’s attention throughout prosecution of ’357’s related applications in the same form Petitioner uses as a reference here (EX1007, 97 (IDS); EX2001, 295), as well as in the form of Grunenwald’s issued patent (EX1007, 10 (“9080211... Grunenwald”); EX2001, 401). Grunenwald is also ***discussed twice in ’357’s specification***—and in one of those passages is ***incorporated by reference***. EX1001, 13:26-33, 14:43. Where a reference has been incorporated by reference and discussed multiple times in the specification, “it is difficult to suggest that the Examiner merely ‘overlooked it’” or

any teaching within it. *See Monolithic*, IPR2020-01348, Pap.19, 11-13. Here, there can be no serious dispute that the Examiner's record of considering Grunenwald was very well developed, and *Becton* factor (d) weighs heavily in favor of discretionary denial.

Petitioner next asserts the Examiner failed to acknowledge the teachings in Grunenwald regarding application of tagmentation in living cells *in vivo*. Pet.68. Petitioner does not cite a single case supporting its argument that the failure of an Examiner to recite or otherwise "acknowledge" every teaching from a reference is material error for *AB* part two. Pet.68. It isn't. *Infra*, §VIII.B.2.

Moreover, Petitioner does not explain how "failing to acknowledge" that teaching was "material error" or would have changed the Examiner's decision to allow the claims. In addition to the Examiner's repeated consideration of Grunenwald, Petitioner also conveniently ignores the prosecution history of the '357's related applications, where the Examiner **explicitly applied art with *in vivo* applications**, directly contradicting Petitioner's assertion of "error" by failing to recognize such teachings in the art. Pet.67-68. In the '250 application, for example, the Examiner acknowledged that Fernandez disclosed tagmentation inside living cells *in vivo* but found that the claims as issued were not anticipated or obvious. EX2001, 380-382 ("Fernandez et al *teach wherein said chromatin is contacted with said insertional enzyme complex within said nucleus of said cell*"),

437-438. Thus, the alleged “teaching” the Examiner purportedly “failed to acknowledge” in Grunenwald was also *clearly acknowledged by the Examiner in Fernandez*. EX2001, 437-438; *Miltenyi*, IPR2022-00853, Pap.11, 45-47 (exercising §325(d) discretion and finding no material error where “substantially the same” teaching petitioner argued was overlooked in its reference was “discussed at length” during prosecution in another reference); *ADT LLC v. Vivint, Inc.*, IPR2022-00612, Pap.8, 24-25 (Aug. 22, 2022) (exercising §325(d) discretion and finding no material error where petitioner did not argue it was error for the claims to issue over the art applied by the examiner in rejections during prosecution, and petitioner’s additional reference disclosed a similar teaching to the art already applied in the rejection). Petitioner does not even *assert* that acknowledgement of this (purported) teaching from Grunenwald would have changed the Examiner’s patentability determination regarding the ’357 claims, let alone *prove* it would. Pet.67-68. Thus, *Becton* factors (e) and (f) weigh heavily in favor of discretionary denial. Petitioner provides no new evidence that warrants reconsideration, as contacting chromatin in a cell nucleus with an insertional enzyme complex was acknowledged by the Examiner (and ignored by Petitioner).

Okino: Similarly, Petitioner’s conclusory assertion that the Examiner “fail[ed] to acknowledge the teachings in... Okino that disclose permeabilization of the cell and nuclear membrane by the use of nonionic detergents, particularly

NP40 and Tween 20,” is, most charitably, baseless. Pet.68. In the ’357’s sole rejection in the file history that *Petitioner submitted here* (EX1007), the Examiner stated that “Jouvenot teaches that permeabilizing of the cell membrane occurs in such a way such that it will not disrupt the structure of the genomic DNA of the cell such that nucleosomal or chromatin structure is not destroyed [0055].

Jouvenot teaches wherein such agents used to permeabilize the cells comprise of NP40, Tween 20 or Triton X-100.” EX1007, 155-156. The Examiner thus *already found and explicitly applied the same teachings* (in Jouvenot) of permeabilizing the cell in such a way that it will not disturb chromatin, including with both of the nonionic detergents (NP40 and Tween 20) that Petitioner now complains were somehow not “acknowledged” because the Examiner did not go through the redundant, unnecessary process of repeating them *again* from a cumulative reference (Okino).²⁴ *Id.* It is not the Examiner who overlooked any teachings—it is Petitioner that conveniently “overlooked” the Examiner’s identical argument and parallel evidence.

Grunenwald in combination with Okino: Finally, Petitioner does not even attempt to explain how the Examiner’s decision would have differed if it had

²⁴ Okino does not disclose permeabilizing a cell nucleus with these agents. *Supra*, §VI.A.

“acknowledged” these disclosures from both Grunenwald and Okino. The Examiner initially argued that Grunenwald and Jouvenot (over which Okino is cumulative) disclosed each limitation (EX1007, 152-158) but then allowed the claims once Applicant pointed out that “Grunenwald fails to ‘expressly teach... a permeabilized cell nucleus,’” that there was no express teaching “of DNA or fragments derived from open chromatin regions,” and that the combination was based on hindsight construction without “first identifying the problem to be solved” (EX1007, 197-200, 224). Petitioner does not explain how the allegedly “overlooked” disclosure from Grunenwald is an “express[] teach[ing]” of a permeabilized cell nucleus (it isn’t), or how Okino arguably remedies any of these failures in a way different from Jouvenot (it doesn’t); nor does Petitioner even identify a problem in Grunenwald that needed remedying such that there would be a motivation to combine these disparate teachings. Pet.66-67; EX1007, 152-158.

Saleh: While Petitioner asserts the Examiner “fail[ed] to acknowledge” the teachings of Saleh, it offers no support for that assertion or any supposed error. Pet.67-68. Petitioner does not, for example, explain how “failing to acknowledge” the teachings of Saleh (which were before the Examiner in the Song reference (EX1007, 187)), cited for dependent claim 29 (which depends from claim 2) in Ground 2, was an error “material to the patentability” of independent claims 1, 16, or 22. AB, 21; Pet.68. In other words, even had the Examiner “acknowledged”

Saleh as Petitioner argues, Petitioner does not dispute that ***claims 1, 16, and 22 would have issued***, as would each of their dependent claims, nor does Petitioner explain how acknowledging Saleh would have impacted claim 2 or any other dependent claim.

2. Petitioner’s Allegation Of “Error” Is Insufficient

Even assuming, *arguendo*, the Examiner somehow “overlooked” Petitioner’s asserted disclosures—an untenable assertion to begin with—Petitioner’s cursory argument under *AB* part two merely states that “the Examiner materially erred by not considering the relevant teachings in Grunenwald and Okino or in Grunenwald and Okino in combination with Saleh” and failed to “consider [Grunenwald’s] *in vivo* embodiment in combination with Okino.” Pet.67. The bare conclusory assertion that the Examiner failed to “acknowledge” a specific Grunenwald embodiment with Petitioner’s cumulative Okino reference is insufficient to meet Petitioner’s burden. At its core, Petitioner’s argument is that an Examiner ***must*** explicitly discuss each and every potentially relevant disclosure from every potential reference to avoid material error. The law requires no such thing. *Ivantis, Inc. v. Sight Scis., Inc.*, IPR2022-01540, Pap.14, 19 (Mar. 22, 2023) (“To the extent Petitioner equates the examiner’s silence in discussing relevant prior art to a material error... we are not persuaded.”); *Eyenovia, Inc. v. Sydnexis, Inc.*, IPR2022-00963, Pap.7, 19 (Nov. 8, 2022) (exercising §325(d) discretion and

finding petitioner failed to show material error where there was no rejection issued over the IPR references but each reference was before the examiner or cumulative of references before the examiner).

Not surprisingly, many cases have similarly made clear that an Examiner need not even make a rejection, let alone provide the detailed analysis Petitioner now demands, to avoid part-two material error. For example, in *Microsoft Corp. v. ThroughPuter, Inc.*, IPR2022-00757, Pap.10, 20-22 (Nov. 1, 2022) the Board explained that the Notice of Allowance demonstrated the Examiner considered petitioner’s primary reference and that the petitioner “does not specifically identify any alleged mistakes made by the Examiner.” The same is true here. The Examiner initially made an explicit Grunenwald rejection but ultimately allowed the claims, explaining in the Notice of Allowance that (as Applicant argued) Grunenwald did not disclose certain limitations, including a permeabilized cell nucleus, and Jouvenot did not render the claimed composition obvious. EX1007, 152-158, 197-200, 224. And Petitioner all but states that the Examiner was correct—Petitioner relies on *Okino* as allegedly disclosing a permeabilized cell nucleus, *not Grunenwald*. Pet.24. Thus, as in *Microsoft*, Petitioner identifies no “mistake” by the Examiner; Petitioner merely wishes the Examiner had discussed several words from another Grunenwald sentence and maintained her rejection. Petitioner has to do far more than express its own disagreement to prove material

error. *Google LLC v. Valtrus Innovations Ltd.*, IPR2022-01197, Pap.9, 23 (Jan. 3, 2023) (exercising §325(d) discretion where petitioner failed to discuss how the examiner erred with respect to the reference with specificity); *Ivantis*, IPR2022-01540, Pap.14, 19; *Motorola*, IPR2022-01287, Pap.11, 22-23; *Eyenovia*, IPR2022-00963, Pap.7, 19.

Thus, both parts of the *AB* test confirm that the Board should exercise its § 325(d) discretion to deny the Petition.

IX. Institution Should Be Denied Under 35 U.S.C. §314(a)

“Even when a petitioner demonstrates a reasonable likelihood of prevailing with respect to one or more claims, ...institution of review remains discretionary.” *Chevron Oronite Co. v. Infineum USA L.P.*, IPR2018-00923, Pap.9, 10 (Nov. 7, 2018) (informative). Indeed, “the Board may consider the *number of claims and grounds that meet the reasonable likelihood standard* when deciding whether to institute *inter partes* review under” § 314(a). *Id.*, at 10-11 (denying institution where “Petitioner demonstrate[d] at most, a reasonable likelihood of prevailing with respect to two dependent claims out of a total of twenty challenged claims”). The same is true here, particularly in light of Petitioner’s many flawed inherency analyses that impact different groups of claims, as well as the additional fundamental failures of Grounds 2-3, which make the analysis of those claims and grounds plainly insufficient to meet the threshold for institution. *See Deeper, UAB*

v. Vexilar, Inc., IPR2018-01310, Pap.7, 42-43 (Jan. 24, 2019) (informative)

(denying institution where “Petitioner demonstrate[d] a reasonable likelihood of prevailing with respect to only two claims on one asserted ground” explaining that “instituting a trial with respect to all twenty-three claims and on all four grounds... would not be an efficient use of the Board’s time and its resources.”); *Nanya Tech.*

Corp. v. Monterey Rsch., LLC, IPR2021-00171, Pap.8, 21-22 (May 26, 2021)

(denying institution where petitioner could “at best demonstrate a reasonable likelihood of success” on “8 of 20 challenged claims”).

Thus, even if, *arguendo*, the Board concludes Petitioner has met its burden for some claims or Grounds, the Board should nevertheless deny institution under §314(a).

X. Conclusion

Petitioner has failed to show there is a reasonable likelihood they will prevail in proving the Challenged Claims unpatentable, and the Petition should be denied in its entirety. In addition, or alternatively, the Board should exercise its discretion to deny the Petition under §§325(d) and/or 314.

Respectfully submitted by:

Dated: September 21, 2023

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PRELIMINARY RESPONSE UNDER 37 C.F.R. §42.107 complies with the type-volume limitation in 37 C.F.R. §42.24(c)(1). According to the word-processing system's word count, the brief contains 13,794 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PRELIMINARY
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